SERONEGATIVE SECONDARY SYPHILIS

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In syphilology, the most secure of the clinical-laboratory correlations has been the impression that secondary syphilis is very nearly always accompanied by a positive serologic test. A statistical study of 13,000 cases of untreated secondary syphilis by Kiesselbach and Eagle in 1946 (1) revealed that 1.7% of these had negative or doubtfully positive serology. Their figures were compiled from data sent to them by the various rapid treatment centers all over the country. Since these were, therefore, mere statistical reports without clinical data, it was suggested that we do a detailed study at our own rapid treatment center to determine the incidence of seronegativity in untreated secondary syphilis.

Despite the universal use of serologic tests in the diagnosis of syphilis since Wassermann, Neisser and Bruch's original work, there are still many unsolved problems in serology. For example, the composition or identity of "reagin", the substance tested for in the serologic tests for syphilis, is still unknown, and may possibly be a product of the reticulo-endothelial system. In fact, it is even uncertain whether the complement-fixation tests and flocculation tests measure the same "reagin".

Serologists have always striven for specificity in the tests for syphilis. This goal is not realized in many cases; the best known examples of this lack of specificity are seronegative primary syphilis, seronegative late symptomatic central nervous system syphilis and biologic false reactions produced by a variety of diseases and other factors.

The literature from 1927 through 1947 on seronegative secondary syphilis is meager. Ten articles, all but one in foreign journals, were found. Four of them (2, 3, 4, 5) dealt with the persistence of secondary syphilis lesions with negative serologic reactions while under treatment. The other six articles (6, 7, 8, 9, 10, 11) reported a total of twelve cases of secondary syphilis with negative serology. Beerman (5) also made reference in his article to literature on seronegative secondary cases prior to 1927.

Medical texts yield surprising variations in the incidence of seronegative secondary syphilis. Fildes (12a) reported the highest figure (10%) while Kampmeier (13) denied the actual existence of such a phenomenon. The authors of the older texts believed that patients with seronegative secondary syphilis had a poorer prognosis in spite of therapy. The tendency to infectious relapse was recorded as being five times more frequent in seronegative than in seropositive secondary

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syphilis (14, 15) (serologic methods of 1917–1925). The detailed data are listed in Table 1. It is of note that the highest incidences were reported in the older literature, possibly because of less sensitive procedures, or because of zone reactions.

Our study is of a retrospective nature, thus reflecting more accurately the actual recorded figures for an "average" rapid treatment center than if an active investigation were undertaken to prove the existence of seronegative secondary syphilis. On the other hand, this had the disadvantage of eliminating rigorous controls that might be set up to prove the presence of this state of syphilis.

A simple definition of seronegative secondary syphilis would be that state of syphilis in which recognized stigmata of the secondary stage are present and darkfield examination is positive, but the serologic tests of standard sensitivity for syphilis are negative.

TABLE 1

The incidence of seronegativity in untreated secondary syphilis

SOURCE	PER CENT INCIDENCE
Fildes (1911) (12a)	10.0
Boas (before 1911) (12b)	3.0
Stokes, Beerman & Ingraham (1944) (15)	1.5
Tobias (1941) (16)	0 to 1.0
Moore (1944) (14)	Probably less than 0.1
Kampmeier (1943) (13)	0.0
Kiesselbach and Eagle (1946) (1)	1.7 (Incl. serodoubtful)

A critical glance will reveal that this definition depends upon and varies with the laboratory tests used and their sensitivity. A laboratory could conceivably use a single serologic test for syphilis or, at the other extreme, use "battery" tests such as those done at the Venereal Disease Research Laboratory, in which several variations of the flocculation test and one or more complement-fixation tests are done. At present, equivalent results with both types are obtained in few laboratories.

Several basic factors may contribute to the erroneous presence of seronegative secondary syphilis in the records of an institution. In our study we found these factors to be responsible: (1) misdiagnosis, (2) false negative serologic tests and (3) clerical and handling errors.

Examples of the error of misdiagnosis would be the co-existence of seronegative primary syphilis with scabies, measles, pityriasis rosea or lichen planus. Multiple primary lesions may also lead to the misdiagnosis of secondary syphilis (17).

False negative serologic reactions could occur as a result of insensitive tests, poor laboratory technic, zone reactions or use of fresh unheated serums.

Errors strictly in the clerical field occur, but also in this group we include losses in handling, switching of specimens due to improper labeling, and any of a number of less possible sources of error in the laboratory, clinic and record room.

MATERIAL

Of the 2,604 cases diagnosed as secondary syphilis in 1946 and 1947 at the West Virginia Medical Center, 51.0% were white females, 34.2% were white males, 7.8% were colored females and 7.0% were colored males. 69% of all the secondary syphilis cases were darkfield positive. 15.2% were relapses and reinfections.

1,732 or 66.1% of the cases were untreated. 74.8% of these untreated cases were darkfield positive.

In conducting this survey the Quantitative Kahn Test, as performed by the West Virginia State Hygienic Laboratory, was used as the index test for selecting cases for further study. This test was the one used in our titered follow-up work and as such was the critical test in any evaluation work done at our center. It was performed on all blood specimens.

RESULTS

Using this method of selection there were 42 cases diagnosed as seronegative secondary syphilis out of the total of 2,604 cases of secondary syphilis, or an incidence of 1.61%. Of the 1,732 cases of untreated secondary syphilis 20 cases were found to be seronegative, or an incidence of 1.15%.

It is known that inadequate treatment of secondary syphilis may cause the positive serologic reaction to revert to negativity. This is a more common occurrence now with the advent of penicillin therapy. Its use in the treatment of gonorrhea, sore throats, unexplained fever or malaise, in rural and metropolitan areas where laboratory facilities are poor, inconvenient, too costly or not utilized, contributes to this situation. The unfortunate practice of giving arsenicals for any penile lesion still occurs. In any event, all cases of secondary syphilis that gave a history of previous treatment with penicillin, an arsenical or bismuth compound, etc. were excluded from this series.

Statistically, then, the incidence of seronegativity in untreated secondary syphilis from our center would be recorded as 1.15%. A more detailed review of the clinical records of these 20 patients reveals many interesting facts.

First we found that three cases were reported as seronegative secondary syphilis because of clerical error. Case #1 resulted from a switch of labels on the specimen tubes in the laboratory; #2 was erroneously abstracted in the record room as having a negative Kahn Quantitative test when it was positive and #3 was abstracted as "secondary syphilis" on the basis of the diagnosis of a previous admission, but at this readmission the patient showed no evidence of syphilis (Table 2).

Second, ten cases belonged to the group with false negative serologic tests, either due to poor laboratory technic or an insensitive Kahn test (Table 2).

Third, seven cases were probably misdiagnosed. Case #14 had scabies previously and extensive residual pigmentation persisted which probably led to the diagnosis of secondary syphilis. The patient was treated on the basis of recent contact with a darkfield positive case.

Cases #15, 16, 17, 18 and 19 were all cases of multiple genital papulo-erosive lesions of short duration with no definite primary lesions. All patients had positive darkfield examinations. All of them showed negative or doubtful flocculation reactions and only two showed positive complement-fixation reactions. None of these patients presented a generalized eruption; the longest duration of lesions was two weeks; all lesions were confined to the genital area and, as near as can be determined from the case records, to the mucous surfaces of the genitals.

TABLE 2

Untreated "seronegativel secondary" syphilis

	W. VA. STATE LABORATORY			W. V. M. C. LABORATORY		
Case No.	Kahn Q.	Hinton	Kol. Wass.	Kahn Std.	Kahn Q.	Mazzini
(1) Cases of Clerical Error						
1	Neg.	Neg.	Neg.	Pos. 4+	Pos. 1:32	Pos.
2	"Neg."	Pos.	Pos.	Pos. 4+	Pos.	Pos.
3	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
(2) Cases of False Negative Serologic Tests						
4	Neg.	N.D.	Pos. 1:40	Pos.	Pos. 1:40	Pos.
5	Neg.	N.D.	N.D.	Pos. 4+	N.D.	Pos.
6	Neg.	Pos.	Pos. 1:8	Pos. 4+	Pos. 1:8	Pos.
7	Neg.	Pos.	Pos. 1:8	Dbt. 1+	N.D.	Dbt.
8	Neg.	Pos.	Pos. 1:8	Pos. 4+	N.D.	Pos.
9	Neg.	N.D.	N.D.	Pos. 3+	N.D.	Pos.
10	Neg.	Pos.	Pos. 1:4	Pos. 3+	Pos. 1:1	Pos.
11	Neg.	Neg.	Pos. 1:8	Dbt. 1+	N.D.	Pos.
12	Neg.	N.D.	N.D.	Pos. 4+	Pos. 1:8	Pos.
13	Neg.	Neg.	Pos. 1:1	Pos. 3+	Pos. 1:2	Pos.

Key N.D.—Not Done

Eroded papules may be either primary or secondary lesions, so the type of lesion lends no definite clue (Table 3).

Previous investigation (17) at this Center of cases diagnosed as primary syphilis indicated that multiple lesions in this stage are much more frequent than is generally conceded. Approximately 40% of the cases of primary syphilis were found to have multiple lesions. Therefore, the authors feel that this group of cases, when all evidence is weighed, fit the diagnosis of primary syphilis with multiple lesions better than the original diagnosis of secondary syphilis.

Case #20 remains as the sole example suggestive of seronegative secondary syphilis in our series. This patient has a history of an eruption and genital lesions of fourteen days duration. Examination on admission revealed a "faded" maculopapular rash on the forearms and "healed" genital papulo-erosions. Darkfield examination of a labial erosion yielded negative results. The patient was treated for syphilis on the basis of a positive darkfield obtained that same day on her marital partner. There was no Jarisch-Herxheimer reaction to treatment. There

TABLE 3

Untreated "seronegative secondary" syphilis

Cases of misdiagnosis

CASE #	W. VA. STATE LABORATORY			W.V.M.C. LABORATORY			TYPE LESIONS	DURATION	SITES	REMARKS
	Kahn Q.	Hinton	Kol. Wass.	Kahn Std.	Kahn Q.	Mazzini				
14	Neg.	N.D.	Neg.	Neg.	Neg.	Neg.	Mucous patches, maculopapules. Dkfld. not done	7 days	Scar & pigmented macules on penis; mucous patches tongue & lip, & maculopapules on trunk, hands, soles.	Scabies. Treated on contact basis. History unreliable: mentally deficient.
15	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Papuloerosions, dkfld. pos.	2 wks.	Vulva.	Multiple papuloerosions.
16	Neg.	Neg.	Pos. 1:1	Neg.	Neg.	Neg.	Papuloerosions, dkfld. pos.	2 wks.	Penis.	Multiple papuloerosions.
17	Neg.	Neg.	Pos. 1:40	Neg.	Neg.	Neg.	Papuloerosions, dkfld. pos.	7–10 da.	Vulva.	Multiple papuloerosions.
18	Neg.	Neg.	Neg.	Pos. 2+	N.D.	Dbt.	Erosions, dkfld. pos.	3 days.	Vulva.	Multiple papuloerosions.
19	Neg.	Neg.	Neg.	Neg.	Neg.	Dbt.	Papuloerosions, dkfld. pos.	1 wk.	Vulva.	Multiple papuloerosions.
20	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Maculopapules & healed erosions, dkfld. neg.	2 wks.	Healed vulvar papuloerosions, maculopapules on forearms.	Husband treated for dkfld. positive primary syphilis.

is nothing in the history to indicate that any cause other than syphilis contributed to the presence of her lesions. Follow-up on this patient and her husband has been completely negative with the exception of a positive Hinton Test on the husband the first month after treatment. The patient was reported five months pregnant, six months post-treatment. Since neither a positive serologic reaction to the tests for syphilis, nor a positive darkfield was obtained, this cannot be accepted as a proven case of secondary syphilis (Table 3).

SUMMARY

A study of 2,604 cases of secondary syphilis, including 1,732 untreated cases, at the West Virginia Medical Center during 1946 and 1947 revealed the following:

1. A 1.61% incidence of seronegative secondary syphilis of all secondary cases recorded with selection based on the Quantitative Kahn Test alone (42 cases).
2. A 1.15% incidence of seronegative untreated secondary syphilis with selection based on the Quantitative Kahn Test alone (20 cases).
3. When all the available clinical and laboratory data relating to these patients was analyzed, not a single case of proven seronegativity in untreated secondary syphilis was found.

CONCLUSIONS

Study of our records indicated that:

1. The majority of cases statistically recorded as seronegative in untreated secondary syphilis are erroneous due to factors of misdiagnosis, false negative serologic tests or clerical error.
2. With modern serologic methods seronegative secondary syphilis is extremely rare, if it exists at all.

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